S/N 09/647,054 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Peter Joseph Cassidy, et al.	Examiner: Christopher M. Gross
Serial No.:	09/647,054	Group Art Unit: 1639
Filed:	March 24, 1998	Docket No.: 707.025US1
Title:	PEPTIDE TURN MIMETICS	

DECLARATION UNDER 37 C.F.R. §1.132

I, Peter Joseph Cassidy, declare and say as follows:

1. I, Peter Joseph Cassidy, received my bachelor's degree with first class honors in 1989 and doctorate degree in 1999 from the University of Queensland, Brisbane, Australia. I am currently a Research Officer at the Institute of Molecular Bioscience of that university and Chief Scientific Officer of Mimetica Pty Ltd. I have authored or co-authored 2 scientific publications, and regularly present work at international symposia (eg Natural Peptides to Drugs April 2006, European Peptide Symposium September 2006). I have over 12 years experience working directly on or supervising work on peptide turn mimetics.

2. I am a named co-inventor of the subject matter claimed in the above-identified patent application and have reviewed the Office Action mailed Apr. 5, 2006 and am familiar with the prosecution history of this application, including the Response filed herewith. I hereby make this Declaration in support of the patentability of the claims of the application.

3. The Examiner has rejected claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138, and 140 on the basis of 35 U.S.C. §102(b) as being anticipated by Ma et al., 1995, Protein Peptide Letters, 2:347-350.

4. Provided herein is a summary of research investigations aimed at duplicating the research of Ma et al as described in the above-cited publication. I participated in or

supervised the collection of these data. These data are submitted to rebut the Examiner's assertion of anticipation of the enumerated claims on the basis of the Ma publication.

5. As outlined in the attached experimental procedures and results shown in the Appendix, I believe based upon convincing evidence that Ma misstated the structure of the reaction product of the final step in the Ma synthesis, the Mitsunobu cyclization that purports to yield the final product **1** from the acyclic precursor **11**. By carrying out the literature reaction, and carefully analyzing spectroscopic data in light of accepted scientific criteria, we have arrived at the conclusion that Ma did not in fact obtain structure **1**, but rather an isomer thereof. Thus, the Ma publication does not describe or enable a successful method for the preparation of a compound of structure **1**, and therefore Ma does not provide a synthetic route to the compound of structure **1**.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statement may jeopardize the validity of this application or any patent issuing therefrom.

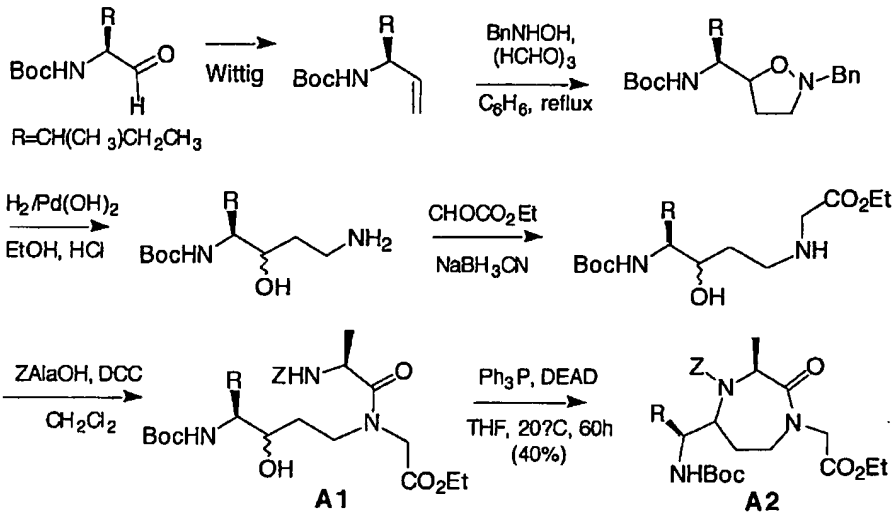
19 September 2006
Date

Peter Joseph Cassidy

APPENDIX

Attempted Repetition of the Synthesis of Ma *et al.*

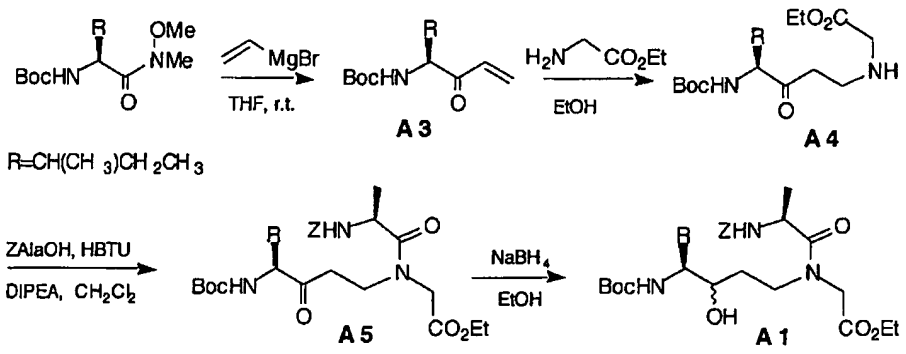
We have repeated the cyclization reaction described by Ma *et al.*, 1995, *Peptide and Protein Letters,* **2**, 347-350, and confirmed by NMR analysis and chemical transformation that the actual product is a structural isomer, not the γ-turn mimetic claimed. The synthesis and analyses and other material in support of the assertion that the method of Ma *et al.* does not represent a reduction to practice are presented below.



Scheme A1 Synthesis proposed by Ma *et al.* for a 1,4-diazepine γ-turn mimetic.

The key step in the proposed synthesis of Ma *et al.* is the cyclization of **A1** (identified as compound **11** in the Ma paper) to the protected target **A2** (identified as compound **1** in the Ma paper) using the Mitsunobu reagents, namely Ph_3P / DEAD. We repeated the synthesis of the cyclization precursor by our own methods as described below.

The alcohol **A1** was more conveniently prepared by the conjugate addition method described earlier than as illustrated in Scheme A1 (4 steps vs. 6 steps). The procedure used is summarized in Scheme A2.



Scheme A2

Thus, the Weinreb amide of Boc isoleucine was reacted with vinyl Grignard in THF to give the α-β unsaturated ketone **A3** by the following procedure: Boc-isoleucine-N-methoxy-N-methylamide (2.25 g, 8.2 mmol) was dissolved in anhydrous THF (20 mL) and cooled to 0 °C under nitrogen. To the stirred solution was added vinyl magnesium bromide in THF (20 mL of a ~1M solution) over 5 min. The reaction was very slow at 0 °C (negligible progress over 1 h), but much faster at room temperature (~70% product after 20 min). After stirring at room temperature for 90 min the reaction was poured into crushed ice/1M HCl and extracted with ether. The organic layer was washed with 0.5M HCl, water, aq. $NaHCO_3$ then brine and then dried over $MgSO_4$. The crude product was formed in good yield and purity and was used directly for the next reaction. TLC 25%EA/light pet. Rf=0.64. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.50, 1H, dd, J = 10, 17 Hz; 6.37, 1H, dd, J = 1, 17 Hz; 5.85, 1H, d, J = 10 Hz; 5.23, 1H, bd, J = 7 Hz; 4.58, 1H, dd, J = 4, 8 Hz; 1.88, 1H, m; 1.45, 9H, s; 1.32, 1H, m; 1.10, 1H, m; 0.98, 3H, d, J = 7 Hz;

0.90, 3H, d, J = 7 Hz. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.0; 155.7; 134.0; 129.6; 79.60; 61.71; 37.50; 28.28 (Boc); 24.09; 16.04; 11.61.

Reaction of **A3** with glycine ethyl ester in ethanol to give **A4** by the following procedure: Glycine ethyl ester hydrochloride (1.0 g, 7.1 mmol) was reacted with **A3** (1.1 g, ~4.7 mmol) and DIEA (450 mg, 3.5 mmol) in ethanol (20 mL) at room temperature overnight. The reaction was diluted with ether (100 mL) and extracted in turn with aq. $NaHCO_3$ and water (x3). Petroleum ether was added (100 mL) and the solution extracted with 0.5M HCl:MeOH 4:1 (x3) (discard the organic layer). The acid washings were immediately neutralised with solid $NaHCO_3$ and then extracted with ethyl acetate and the ethyl acetate layer washed with water then brine and then dried over $MgSO_4$. Evaporation of the solvent *in vacuo* left 800 mg (~50%) of crude product of sufficient purity for use in the next reaction. TLC EtOAc Rf=0.52. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 209.0; 171.7; 155.8; 79.57; 63.95; 60.76; 50.67; 43.69; 40.82; 36.74; 28.19 (Boc); 24.05; 16.01; 14.08; 11.51. Mass Spectrum (ISMS) m/z 345 (MH^+), calculated for $C_{17}H_{32}N_2O_5$: 344.

The amino ketone **A4** (690 mg, 2 mmol) was then coupled with Z-alanine to give **A5** using standard solution phase coupling procedure with HBTU reagent and DIEA in CH_2Cl_2/THF. The crude product was purified by flash chromatography eluting with 30% EtOAc in light petroleum for a yield of 94% (1.03 g). TLC EtOAc:light pet. 1:2 Rf=0.25. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.34, 5H, m; 5.68, 1H, bm; 5.18-5.02, 3H, m's; 4.72, 0.5H, m; 4.48-4.07, 5H, m's; 3.88-3.54, 2.5H, m's; 2.75-2.05, 2H, m's; 1.89, 1H bs; 1.44, 1.43: 9H, 2s, Boc; 1.38, 1.5H, d, J = 6.9 Hz (alaHβ, one rotamer); 1.34-1.28, 5.5H, m's; 1.07, 1H, m; 1.00-0.82, 6H, m's. **^{13}C NMR** (75 MHz, $CDCl_3$), signals due to the equivalent carbon in different rotamers are grouped in parentheses where possible: δ (209.0, 207.9); (173.39, 173.25); (169.15, 168.84); 155.75, 155.67, 155.56, 155.33: carbamate signals; 136.20; 128.31; 127.91; 127.80; (79.72, 79.57); 66.60; (64.01,

63.85); (61.61, 61.09); (50.96, 48.65); (46.63, 46.57); (43.75, 43.23); (40.02, 39.07); (36.56, 36.29); 28.14 (Boc); (24.09, 24.03); 18.74; 15.92; 13.85; (11.44, 11.38). Mass Spectrum (ISMS) m/z 550 (MH^+), calculated for $C_{28}H_{43}N_3O_8$: 549

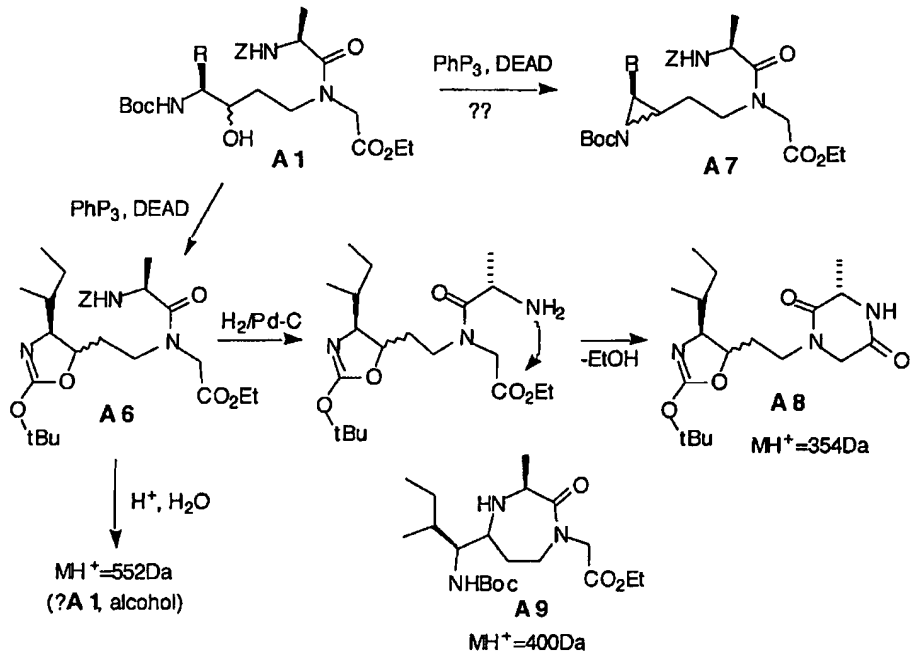
The ketone **A5** (430 mg, 0.78 mmol) was dissolved in ethanol (5 mL) and $NaBH_4$ (15 mg, 0.40 mmol) added to the stirred solution at room temperature, and stirring continued for 1 h. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate and washed with 1M HCl, water, aq. $NaHCO_3$, brine and then dried over $MgSO_4$. The residue after solvent evaporation was purified by flash chromatography eluting with ethyl acetate:light petroleum ~1:1 (some separation of diastereomers occurred) for an approximately quantitative yield of the alcohol **A1**. TLC EtOAc:light pet. 1:1 Rf=0.28. **^{1}H NMR** (300 MHz, $CDCl_3$), late eluting fractions, rotamers/diastereomers >2:1: δ 7.39-7.29, 5H, m; 5.80, 1H, d, J=9 Hz; 5.15, 1H, d, J=12 Hz; 5.11-5.49, ~1H, m; 4.96, ~1H, d, J=12 Hz; 4.67-4.42, ~1H, m's; 4.19, ~2H, bq, J=7.2 Hz; 4.03-3.88, ~2H, bm; 3.88-3.40, ~4H, m's; 3.30-3.09, 1H, m; 1.96-1.66, ~2H, m; 1.55, ~1H, m; 1.42, 9H, s, (Boc); 1.331.33, d, J=7 Hz; 1.28, t, J=7.2 Hz; 1.15, d (minor isomer), J=6.8 Hz; 1.37-1.05 ~8H; 1.0-0.82, ~6H, m's. **^{13}C NMR** (75 MHz, $CDCl_3$), major peak only shown unless otherwise indicated: δ 174.0; 169.0; 156.4; 156.3; 135.9; 128.4; 128.1; (128.0, minor isomer); 127.9; 78.92; 66.96; (66.56, minor isomer); 66.11; 61.26; 59.49; 47.74; 46.10; 45.24; 34.38; 31.31; 28.30 (Boc); 22.29; 18.85; 16.41; 14.00; 11.90. Mass Spectrum (ISMS) m/z 552 ($M+H^+$), calculated for $C_{28}H_{45}N_3O_8$: 551

The alcohol **A1** was reacted with the Mitsunobu reagents as described by Ma *et al.* (Scheme 4.37) as follows: The alcohol **A1** (150 mg, early eluting fraction) was dissolved in dry THF and triphenylphosphine (71 mg) added. To the stirred solution at room temperature under nitrogen was added DEAD (43 uL), and stirring continued for 24 h. Analysis of the crude reaction revealed the formation of a dehydration product ($M+H^+$=534 Da) in moderate yield. Another equivalent of triphenylphosphine/DEAD

was added and stirring continued for a further 48 h. The solvent was removed *in vacuo* and the residual oil dissolved in ether/petroleum ether and left to stand to encourage the precipitation of the triphenylphosphine oxide and diethoxycarbonyl hydrazine (white solid, filtered off). The oil remaining after evaporation of the filtrate was purified by flash chromatography eluting with petroleum ether and 10-100% ether in petroleum ether, yield was ~40% (60 mg). TLC ethyl ether Rf=0.61. The NMR spectra were quite complex, as may be expected from the possible mixture of diastereomers/ rotamers. However, it was possible to clearly identify the alanine spin system with Hα at 4.71ppm (1H, broad pentuplet, J~8Hz). 1D decoupling experiments were performed: irradiation at 4.7ppm caused the collapse of two signals to singlets, a doublet centred on 1.40ppm (J=7Hz, alanine Hβ), and a broad doublet (1H, J=8Hz) at 5.62ppm (alanine NH). These assignments were confirmed by irradiation at 1.4ppm which caused collapse of the multiplet at 4.71ppm to a doublet with J=8Hz. The presence of the NH proton in the alanine spin system rules out the γ-turn mimetic **A2** proposed by Ma *et al.* as a possible structure for the product, and leaves open the possibility of **A6** or **A7** (Scheme A3) which we felt were more probable products, as the true structure. **^{1}H NMR** (300 MHz, $CDCl_3$): (selected peaks) δ 5.62, ~1H, bd, J=8 Hz; 4.71, ~1H, m(q); 1.40, d, J=6.8 Hz. Decoupling experiments: irradiate 1.4 ppm -> 4.71 = doublet, J=8 Hz; irradiate 4.71 ppm -> 1.4 = singlet, 5.62 = singlet. **^{13}C NMR** (75 MHz, $CDCl_3$): the spectra were difficult to analyse due to the presence of rotamers/diastereomers, peak broadening and impurities which co-eluted. There were a couple of notable features: (i) the appearance of a new peak at the relatively unusual shift of 160.7 ppm possibly due to the carbamate derived oxazoline carbon (only one carbamate resonance was observed, 155.5 ppm), and (ii) the downfield shift of the tertiary Boc carbon resonance which was observed at 81.22 ppm, whereas NHBoc tertiary carbon shifts are normally at a shift upfield of 80 ppm (e.g.

78.9 in the alcohol precursor). Mass Spectrum (ISMS) m/z 534 (MH^+), calculated for $C_{28}H_{43}N_3O_7$: 533

To confirm the results of the NMR analysis a further experiment was carried out. The product material was hydrogenated (EtOH, Pd-C) to remove the Z group. If the product has structure **A6** or **A7** then the amine will now be free to form the diketopiperazine **A8**, a facile reaction in such a system, Scheme A3. If any of the target γ-turn mimetic **A2** is present then it will be deprotected to the (very stable) free amine **A9** and be easily detected in the ionspray mass spectrum (ISMS). Analysis of the product mixture from the hydrogenation revealed the presence of a mass peak corresponding to the diketopiperazine (MH^+=354Da), but no trace whatsoever of **A9** (MH^+=400Da).

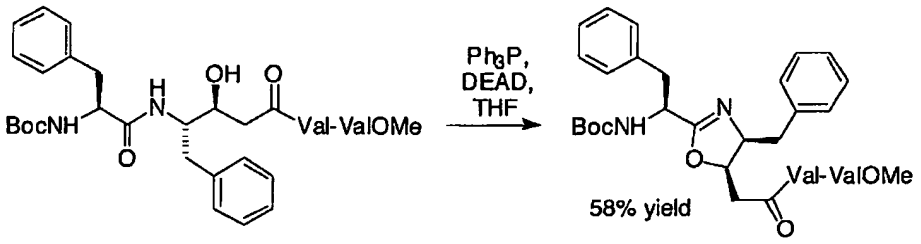


Scheme A3

Finally, it was also observed that the cyclization product (which we propose to be **A6**) was easily hydrolysed by dilute aqueous acid (e.g. room temperature 0.1% aq. TFA, 12h), back to the alcohol **A1** (or a compound of the same mass). This last observation is

more consistent with the product structure being the oxazoline **A6** rather than the aziridine **A7** as the oxazoline is more probably subject to facile hydrolysis by aqueous acid, the facile hydrolysis is entirely inconsistent with the structure **A2** proposed by Ma *et al.*

In further support of **A6** as the product structure, peptide alcohols similar in structure to **A1** have been reported to form oxazolines (Galéotti, Montagne *et al.* 1992), for example:



Other evidence against formation of **A2** by the Mitsunobu reaction as proposed by Ma *et al.* is presented below:

(1) Difficulty of forming seven membered rings via the Mitsunobu reaction

(a) Literature precedent

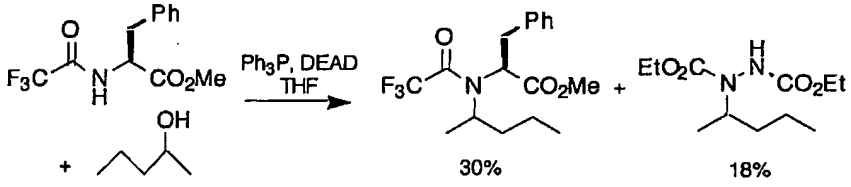
The literature on the formation of cyclic amines and amides with the Mitsunobu reaction contains numerous examples of the formation of 3-6 membered rings (Carlock and Mack 1978; Robinson, Barry *et al.* 1983; Pfister 1984; Kelly, Eskew *et al.* 1986; Henry, Marcin *et al.* 1989; Bernotas and Cube 1991), but very few cases of seven membered ring formation. In one paper on the cyclization of amino alcohols the faliure to form a simple seven membered target is specifically described.(Bernotas and Cube 1991) In the organic reactions entry on the Mitsunobu reaction (Hughes 1992) three instances of seven membered ring formation with carbon-nitrogen bond formation are

described: all three involve a primary alcohol, two occur in polycyclic systems and appear to be special cases, and the third involves alkylation of a hydroxamide - far easier than an amide due to higher NH acidity.

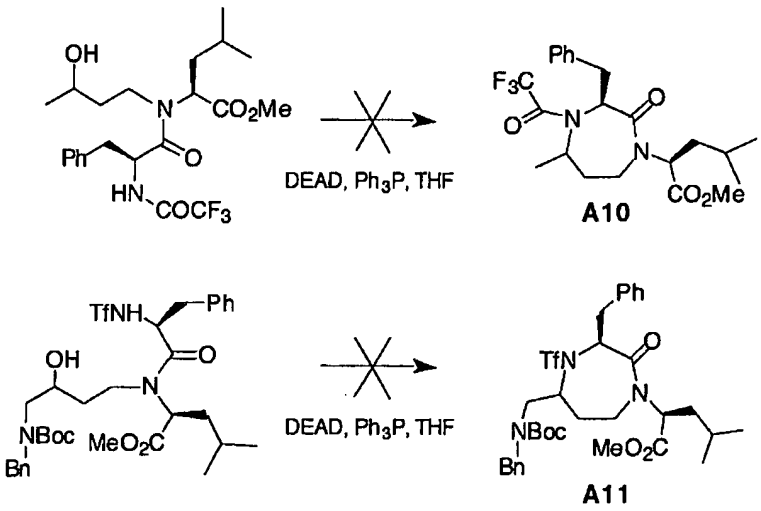
There appears to be no literature precedent for the formation of a seven membered ring to a simple amide or carbamate nitrogen. In addition there is little precedent for secondary amide N-alkylation with hindered secondary alcohols, as is proposed to occur in the formation of **A2**.

(b) Synthetic studies

Extensive studies on the use of the Mitsunobu reaction for the formation of the target system were carried out in our laboratories prior to becoming aware of the proposed synthesis. In our hands this approach was ineffective. The key reactions are described in Schemes A4 and A5.



Scheme A4

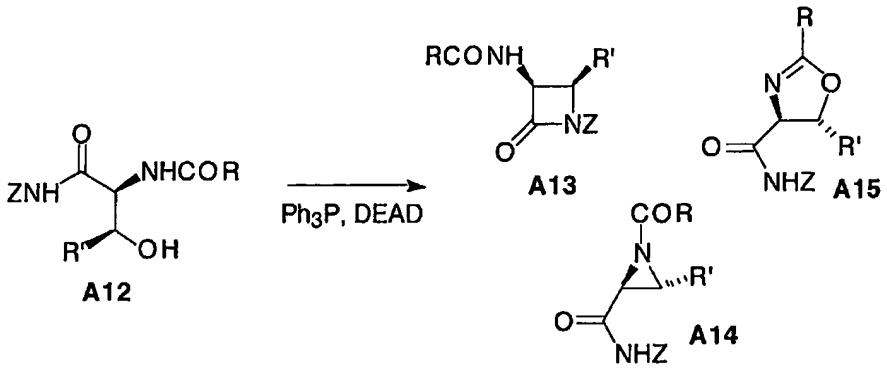


Scheme A5

The formation of the alkylation product was somewhat successful in the intermolecular reaction (Scheme A4), but this success was not repeated in cyclic systems (Scheme A5). No significant amount of the target cyclic products **A10** or **A11** was detected.

(2) Competing reactions - oxazoline and aziridine formation.

Cyclization of β-hydroxy amide derivatives A12 with the aim of forming β-lactams **A13** also results in the formation of the aziridine **A14** and oxazoline **A15** products shown in Scheme A6.(Hughes 1992) Another example of oxazoline formation was described above.(Galéotti, Montagne *et al.* 1992)



Scheme A6

As the Mitsunobu reaction is relatively effective for the formation of small ring sizes, it is quite probable that the formation of aziridines and oxazolines will compete with other possible cyclization s, other factors being equal. Such competition can take place in the proposed synthesis, the products would then be **A6** and/or **A7**, Scheme A3. Both the aziridine and oxazoline are isomeric with the target compound **A2**, possibly leading to their confusion with the target, a situation easily resolved by ^{1}H NMR as we demonstrated above.

We also note that there was a publication after the filing date of the present application from the same laboratory, namely the *"Laboratoire des Aminoacides, Peptides et Protéines, UMR 5810 CNRS-Universités Montpellier I et II.* Nouvet et al., *Tetrahedron* 1999, **55**, 4685-4698. This document shares a common author with the earlier Ma paper, namely René Larzaro. The applicants respectfully point out for the Examiner's attention that this publication in fact contradicts the Ma publication. The paper describes the synthesis of the γ-turn mimetics using a sulphonamide group in place of the Z (benzyloxycarbonyl) group in cyclization akin to the cyclization allegedly carried out by Ma. Importantly for the purposes of the disclosure in Ma this document specifically notes on page 4687, lines 3 to 4, that the *"sulfonamide group was found to be*

essential for the cyclization step : other tested N-substituents (-Z, -Troc, or -Ac, unpublished results) were inefficient whatever the redox system was used". This paper by Nouvet further supports the contention that the Z group as used in the earlier Ma paper would not in fact work for cyclizations of this type.

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